PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference H1566 PCT S3	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/004076	International filing date *(day/month/year)* 16.04.2004	Priority date *(day/month/year)* 17.04.2003

International Patent Classification (IPC) or national classification and IPC
C12N15/12, C12N15/11, C12N5/10, C12N1/21, C12Q1/68, C07K16/28, A61K31/40, A61K38/17, A61K39/395, A61K31/7088, G01N33/68

Applicant
AFFECTIS PHARMACEUTICALS AG et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 12 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 10 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.11.2004	18.07.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/004076

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-149 as originally filed

Sequence listings part of the description, Pages

1-62 as originally filed

Claims, Numbers

1-29 received on 17.02.2005 with letter of 16.02.2005

Drawings, Sheets

1/41-41/41 as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☒ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☒ the claims, Nos. 30-56
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 11-15,17,29
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/004076

Box No. II Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
   - ☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
   - ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

   see separate sheet

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 18-21,26-28 with respect to industrial applicability

   because:

   ☒ the said international application, or the said claims Nos. 18-21,26-28 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

   ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

   ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

   ☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☒ restricted the claims.
   - ☒ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-28
	No:	Claims	29
Inventive step (IS)	Yes:	Claims	1-28
	No:	Claims	29
Industrial applicability (IA)	Yes:	Claims	1-29
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item II.

The present application is regarded as having a valid priority of 17.04.2003.

Re Item III.

Claims 18-21 and 26-28 relate to subject matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of these claims (Art. 34(4)(a)(I) PCT).

Re Item IV.

The subject matter of claim 29 is a diagnostic composition comprising i.a. polymorphic nucleic acid molecules of P2X7R as defined in claim 11.

P2X7R polymorphisms have been well documented in the prior art as well as the diagnosis and treatment of affective diseases, see for example:

(1) EP1199372 (P2X7R polymorphisms)
(2) WO0162787 (affective diseases)

In (1) on pp.9 and 15 i.a. a mutation at position 270 of the amino acid sequence is disclosed which is identical to one of the mutations claimed in claim 1(b), Table A of the present application. This document discloses implications of polymorphisms of the P2X7 receptor gene in diseases which are **not** affective diseases (p.2, lines 10-19).

The difference between this prior art document and the present application is the provision of further polymorphisms in said gene. The technical effect is the possibility to detect affective disorders and the problem to be solved is the provision of tools for diagnosing and treating affective disorders.
This problem is known in the art, see (2). However, no link can be seen in the art between

polymorphisms of the P2X7 gene and their use in diagnosing and treating affective diseases. Therefore, the use of the plurality of polymorphisms in detecting affective diseases would be a special technical feature and unitary under Rule 13.1 PCT.

But for the **compounds** (claim 29), i.e. the polymorphic nucleic acids and polypeptides per se, the following applies in analogy to the PCT Guidelines 10.17 ("Markush Practice"), 10.55 and 10.56 (examples 35, 36):

A same or corresponding technical feature shared among said claimed compounds resides in their common property (diagnostic for affective diseases) and their shared structural element that is essential to the common property (mutants/polymorphisms of the P2X7 gene). However, polymorphisms of the P2X7 gene are known in the prior art (see above, document (1) discloses even at least one polymorphic amino acid exchange claimed in the present application at position 270). Therefore, the subject matter of claim 29 is not new under Art. 33(2) PCT in view of (1) as the polymorphic nucleic acid molecules of (1) are suitable for the purpose of claim 29 of the present application (see Guidelines 5.23).
Within claim 29, the structural relationship between the compounds is not new and consequently, the technical feature of the compounds is not special and the common property alone is not sufficient to establish unity among the different compounds. As a consequence, there is no single inventive concept underlying the plurality of claimed inventions of the present application in the sense of rule 13.1 PCT and the different inventions (all different compounds of claim 29), not belonging to a common inventive concept, are formulated as the different subjects on the communication pursuant to Art. 17(3)(a) PCT.
Accordingly, the methods as defined in claims 1 to 28 form the first invention, and each of the diagnostic compositions defined in claim 29 forms a separate invention.

Concerning the subject matter of claim 29 examination is restricted to the compound that has been subject to International Search.

Re Item V.

The following document is referred to in this communication:

D1: EP-A-1 199 372 (ASTRAZENECA AB) 24 April 2002 (2002-04-24)
D2: WO 01/62787 A (OXFORD GLYCOSCIENCES UK LTD ; HERATH HERATH MUDIYANSELAGE AT (GB); PAR) 30 August 2001 (2001-08-30)
D3: US-B1-6 214 581 (LYNCH KEVIN J ET AL) 10 April 2001 (2001-04-10)

1 Amendments (Art. 28 PCT)

An amended set of claims has been filed with the letter dated 16.02.2005. The subject matter of new claim 11 is the use of various nucleic acid molecules for the preparation of a diagnostic composition to diagnose affective diseases. This claim is a combination of original claims 1, 23 and 26. The subject matter of claim 11 (ii), (v) and (vi) are vectors, aptamers and primers comprising or binding or amplifying nucleic acid molecules of (i), which comprises (a) to (m). This specific combination of each of (ii), (v) and (vi) with (m) is not derivable from the application as filed and is therefore unallowable under Art. 28(2) PCT. The same applies to the subject matter of new claims 12, 13, 17 and 29 as far as they relate back to new claim 11(m), to the subject matter of new claims 14 as far as it relates back to anything different from claim 11(b) and (d) and to the subject matter of new claims 15 as far as it relates back to claim 11.

2 Patentability (Rule 67(1) PCT)

For the assessment of the present claims 24-27, 30, 34, 35, 54-56 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for

the manufacture of a medicament for a new medical treatment.
The problem of said claims is the formulation: the wording of the claims is such that the scope of said claims comprises or does not exclude the step of obtaining the sample which is an in vivo step, i.e. the method is not restricted to steps to be performed solely on a sample.

3 Novelty (Art. 33(2) PCT)

3.1 The subject matter of claims 1 to 28 is considered novel under Art. 33(2) PCT in view of the available prior art under PCT regulations.

3.2 Document D1 discloses on pp.9 and 15 i.a. a mutation at position 270 of the amino acid sequence which is identical to one of the mutations claimed in claim 1(b), Table A of the present application rendering the subject matter of claim 29 not new under Art. 33(2) PCT in view of D1 as the polymorphic nucleic acid molecules of D1 are suitable for the purpose of claim 29 of the present application (see Guidelines 5.23).

4 Inventive Step (Art. 33(3) PCT)

4.1 Document D3 is the closest prior art concerning the subject matter of claim 1 to 28 and discloses in general P2X and P2Y purinoreceptors (also mentions P2X7, col. 5, 2nd par.) being involved i.a. behavioural disorders (among many others) such as i.a. depression (col. 3 last par.) and their use in identifying agonists and antagonists for each purinoreceptor subtype for therapeutic purposes (col. 4, 2nd par.).
From this, the subject matter of present claims 1 to 28 differs in that polymorphic forms of P2X7R are disclosed which are diagnostic for affective disorders and that modulating the activity of P2X7R is suitable to treat said disorders.
The problem to be solved is the provision of means to diagnose and treat affective disorders.
The very general disclosure of D3 leaves open which receptor is to be selected for modulation in order to treat a disease and leaves open which of the several diseases is to be treated. As a consequence, the skilled person seeking to solve the problem posed

would not be guided to the solution of present claims 1 to 28 using D3 in an obvious manner rendering the subject matter of claims 1 to 28 inventive under Art. 33(3) PCT in view of the available prior art because other documents teaching P2X7R polymorphisms do not disclose a link to affective diseases.

4.2 D1 is the closest prior art for invention No. 2 (claim 29, diagnostic composition) and discloses several polymorphism in the P2X7 gene from which the subject matter of invention 1 of the present application differs in that a different mutational/polymorphic position is disclosed. The technical effect that was alleged in the present application to be associated with said difference is its use in diagnosis and treatment of affective diseases. There is no prior art pointing to said mutation and to said use. In principle, this could substantiate an inventive step under Art. 33(3) PCT for the subject matter of present claim 29 with respect to the polymorphism searched.
However, in the description at pages 124 to 133 an allelic and genotypic association with diseases has only been shown for some exonic sites (p.129, 132/133 resp.) but not for position 362 presently under examination.
At present, no technical effect has been shown concerning position 362 with respect to detection and treatment of affective diseases. As a consequence, the problem to be solved is reduced to the simple provision of a further P2X7R polymorphism which is not inventive under Art. 33(3) PCT in view of D1. Therefore, the subject matter of claim 29 (invention No.2) is not inventive under Art. 33(3) PCT.

5 Industrial Application (Art. 33(4) PCT, inventions 1, 40 and 41)

The subject matter of present claims 1 to 29 is industrial applicable under Art. 33(4) PCT with respect to the inventions examined (see above).

6 Clarity, Support, Disclosure (Art. 5, 6 PCT)

6.1 The subject matter of claims 1 and 2 is directed to the use of modulators and agonists of P2X7R.
Normally, it is regarded as an undue burden to isolate and characterise all potential

agonists/antagonists without any effective pointer to their identity as the skilled person would have to test every known compound and every conceivable future compound for its activity to see if it falls within the scope of said claims. Also the compound classes disclosed in the application are of no help as their applicability for the claimed use is speculative. A technical effect has only been shown for known modulators of P2X7R.

On the other hand, the applicant's arguments can be followed that this application discloses for the first time a link between agonists of P2X7R and affective diseases. The contribution to the art justifies a broad protection of the principle. As the modulator target is a well defined protein and an assay for agonist detection is disclosed (p.142 and is also known in the prior art), it can indeed be seen as routine to identify new agonists via High Throughput Screening. A limitation to concrete agonists known in the art could be regarded as an undue limitation.
However, it is emphasized that any argument of the applicant based on decisions of a Board of Appeal of the EPO or on the EPO's Guidelines is without substance as the present case is to be judged under PCT regulations.
Only for the sake of completeness and in case the applicant continues in the regional phase it is pointed out that T 68/85 does not apply here because in that decision the nature of the compounds used was well defined and it was only their ratio that was important for the technical effect. The experimental burden to put the invention into practise is therefore much narrower than in the present case, where a modulator is to be identified from an indefinite group of compounds.
However, due to the above facts relating to the contribution to the art and the technical possibilities in the filed, it is acknowledged that the use of an agonist to prepare a composition for treating an affective disorder (i.e. the subject matter of claim 2) is regarded as fulfilling the requirements of Art. 5 and 6 PCT.
This does not apply to the subject matter of claim 1 as a the term "modulator" also comprises antagonists which do not work in that respect as shown in example 10. The nature of the modulator as being an agonist is an essential technical feature that is absent from claim 1 rendering said claim not supported and disclosed under Art. 5 and 6 over the whole scope claimed.

6.2 The subject matter of claims 11(iv), (v), 14 and 15 relates to antibodies and aptamers that specifically bind to the claimed polymorphic P2X7R. "Specific binding" is understood

to mean an antibody or aptamer that does not recognize any other protein which means that said antibody can differentiate between two proteins that differ by only one amino acid residue. The generation of such antibodies is not considered a routine matter given the labour intensive exclusion of cross reactivity of the candidate specific antibody with the same protein differing only by one amino acid. This leads to an undue burden for the skilled person trying to put the invention into practise as there is also the possibility that the generation of such extremely specific antibodies fails. Therefore, the subject matter of said claims is not disclosed in an enabling manner unless concrete antibodies/aptamers showing said extreme specificity are disclosed in the application. As no such antibody or aptamer was disclosed in the application, said claims and related dependant claims fail the disclosure criterion set forth in Art. 5 PCT).

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO03042190	22.05.2003	30.09.2002	12.11.2001

PCT/EP2004/004076
NeuroNova AG
Our Ref.: H1566 PCT S3

CLAIMS

1. Use of a modulator of P2X7R activity for the preparation of a pharmaceutical composition for treating an affective disorder.

2. The use of claim 1, wherein said modulator is an agonist.

3. The use of claim 2, wherein said agonist is selected from the group consisting of ATP, ATP-4 and BzATP (2'-3'-O-(4-Benzoylbenzoyl)adenosine 5'-triphosphate ($C_{24}H_{24}N_5O_{15}P_3$)).

4. Use of tenidap ($C_{15}H_{11}ClN_2O_2S$) or a derivative thereof or 3-substituted-2-oxindole-1-carboxamides for the preparation of a pharmaceutical composition for treating an affective disorder.

5. The use of any one of claims 1 to 4, wherein said pharmaceutical composition optionally further comprises a β-adrenergic receptor modulator.

6. The use of claim 5, wherein said β-adrenergic receptor modulator is a β-adrenergic receptor antagonist selected from the group consisting of DL-propanolol, D-propanolol and labetolol.

7. The use of any one of claims 1 to 6, wherein said affective disorder is selected from the group consisting of major depression, generalized anxiety disorder and bipolar disorder.

8. The use of claim 7, wherein said major depression is selected from the group consisting of major depression, dysthymia, atypical depression, premenstrual dysphoric disorder and seasonal affective disorder.

9. The use of claim 7, wherein said generalized anxiety disorder is selected from the group consisting of panic disorder, phobias, agoraphobia, social phobia, specific phobia, obsessive-compulsive disorder, post-traumatic stress disorder, separation anxiety disorder, mania, hypomania and cyclothymic disorder.

10. The use of claim 7, wherein said bipolar disorder is bipolar disorder type I or bipolar disorder type II.

11. Use of

(i) a nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of:

(a) a genomic nucleotide sequence encoding an ATP-gated ion channel P2X7R and which contains a mutation in the 5'UTR region corresponding to positions 362, 532, 1100, 1122, 1171 or 1702 of the genomic sequence of the wild-type ATP-gated ion channel P2X7R as depicted in SEQ ID NO: 1, wherein at said position said nucleotide is replaced by another nucleotide;

(b) a nucleic acid sequence encoding a polypeptide which has an amino acid sequence of the ATP-gated ion channel P2X7R, wherein in the exon as indicated in column "Exon" of the following Table A the amino acid residue as indicated in column "Amino acid residue" of Table A corresponding to the position as indicated in column "Position in wild-type" of Table A of the wild-type ATP-gated ion channel P2X7R amino acid sequence as depicted in SEQ ID NO: 3 or 4 is replaced by another amino acid residue

Table A

Exon	Amino acid residue	Position in wild-type
exon 3	R (Arg)	117
exon 5	G (Gly)	150
exon 6	E (Glu)	186

exon 6	L (Leu)	191
exon 8	R (Arg)	270
exon 13	I (Ile)	568
exon 13	R (Arg)	578

(c) a nucleotide sequence encoding an ATP-gated ion channel P2X7R and which contains a mutation in exon 5 or 8 corresponding to position 32548 or position 37633 of the wild-type ATP-gated ion channel P2X7R nucleotide sequence as depicted in SEQ ID NO: 1, wherein at said position said nucleotide is replaced by another nucleotide

(d) a nucleic acid sequence encoding a polypeptide which has an amino acid sequence of an ATP-gated ion channel P2X7R, wherein amino acids corresponding to positions 488 to 494 of the wild-type ATP-gated ion channel P2X7R as depicted in SEQ ID NO: 3 or 4 are deleted;

(e) a genomic nucleotide sequence encoding an ATP-gated ion channel P2X7R, wherein in the intron as indicated in column "Intron" of the following Table B the nucleotide as indicated in column "Replaced nucleotide" of Table B corresponding to the position as indicated in column "Position in wild-type" of Table B of the wild-type ATP-gated ion channel P2X7R nucleotide sequence as depicted in SEQ ID NO: 1 is replaced by another nucleotide

Table B

Intron	**REPLACED NUCLEOTIDE**	**Position in wild-type**
intron 1	G	3166
intron 1	C	24778
intron 1	C	24830
intron 3	A	26308
intron 3	G	26422

intron 4	G	32394
intron 4	T	32434
intron 5	A	32783
intron 6	G	35641
intron 6	A	35725
intron 6	T	36001
intron 7	G	36378
intron 7	T	36387
intron 7	G	36398
intron 9	C	47214
intron 11	T	47563
intron 12	C	54307
intron 12	G	54308

(f) a genomic nucleotide sequence encoding an ATP-gated ion channel P2X7R and which contains a mutation in the 3'UTR region corresponding to position 54925, 55169, 55170, 55171 or 55917 of the wild-type ATP-gated ion channel P2X7R nucleotide sequence as depicted in SEQ ID NO: 1, wherein at said position said nucleotide is replaced by another nucleotide;

(g) a nucleotide sequence comprising at least 20 or 21 nucleotides and comprising the mutations or deletions as defined in any one of (a) to (f);

(h) a nucleic acid sequence comprising a nucleotide sequence as shown in any one of SEQ ID NOs: 13 to 51;

(j) a nucleic acid sequence encoding a polypeptide comprising the amino acid sequence of SEQ ID NOs: 5 to 12;

(k) a nucleotide sequence which hybridizes to a nucleotide sequence defined in any one of (a) to (g) or to the nucleotide sequence of (h) and having a mutation as defined in any one of (a) to (f); and

(l) a nucleic acid sequence being degenerate as a result of the genetic code to the nucleic acid sequence as defined in (j);

(m) a genomic nucleotide sequence having a nucleotide replacement or deletion selected from the following Table C indicating in column "Region of P2X7R" the region of the P2X7R genomic nucleotide sequence in which the replacement or deletion occurs, in column "Nucleotide" of Table C the nucleotide which is replaced by another nucleotide or the nucleotides which are deleted and in column "Position in wild-type" of Table C the corresponding position in the nucleotide sequence of the wild-type ATP-gated ion channel P2X7R as depicted in SEQ ID NO: 1

Table C

Region of P2X7R	NUCLEOTIDE	Position in wild-type
5'UTR	T	362
5'UTR	T	532
5'UTR	A	1100
5'UTR	A	1122
5'UTR	C	1171
5'UTR	T	1351
5'UTR	G	1702
5'UTR	T	1731
5'UTR	C	1860
5'UTR	C	2162
5'UTR	C	2238
5'UTR	A	2373
5'UTR	G	2569
5'UTR	G	2702
intron 1	G	3166
intron 1	C	24778
intron 1	C	24830
exon 2	T	24942
exon 3	C	26188

exon 3	A	26308
exon 3	G	26422
intron 4	G	32394
intron 4	T	32434
exon 5	G	32493
exon 5	G	32506
exon 5	C	32507
exon 5	C	32548
intron 5	A	32783
intron 5	T	35309
intron 5	C	35374
intron 5	A	35378
exon 6	G	35438
exon 6	T	35454
intron 6	T	35549
intron 6	G	35641
intron 6	A	35725
intron 6	T	36001
intron 6	A	36064
intron 6	deletion of GTTT	36091 to 36094
intron 6	C	36108
intron 7	C	36374
intron 7	G	36378
intron 7	T	36387
intron 7	G	36398
intron 7	C	37439
intron 7	T	37513
exon 8	C	37604
exon 8	G	37605
exon 8	G	37623
exon 8	C	37633
intron 9	C	47214

exon 11	G	47383
exon 11	C	47411
intron 11	T	47563
intron 12	C	54307
intron 12	G	54308
exon 13	C	54399
exon 13	A	54480
exon 13	C	54523
exon 13	deletion of CCCTGAGAGCCACAGGTGCC T	54562 to 54582
exon 13	A	54588
exon 13	C	54664
exon 13	G	54703
exon 13	A	54804
exon 13	G	54834
exon 13	G	54847
3'UTR	G	54925
3'UTR	C	55169
3'UTR	A	55170
3'UTR	A	55171
3'UTR	C	55917

(ii) a vector comprising the nucleic acid molecule of (i);

(iii) a polypeptide encoded by the nucleic acid sequence of (i)(b) or (i)(d);

(iv) an antibody specifically directed to the polypeptide of (iii);

(v) an aptamer specifically binding to the nucleic acid molecule of (i); and/or

(vi) a primer or pair of primers capable of specifically amplifying the nucleic acid molecule of (i)

for the preparation of a diagnostic composition for the detection of an affective disorder.

12. The use of claim 11, wherein said nucleic acid molecule is derived from mouse, rat or human.

13. The use of claim 11 or 12, wherein said nucleic acid molecule is DNA, RNA, PNA or phosphorothioates.

14. The use of claim 11, wherein said antibody specifically reacts with an epitope generated and/or formed by the mutation in the ATP-gated ion channel P2X7R selected from the group consisting of:

(i) an epitope specifically presented by a polypeptide which has an amino acid sequence of an ATP-gated ion channel P2X7R, wherein the R (Arg), G (Gly), E (Glu), L (Leu), R (Arg), I (Ile) or R (Arg) residue corresponding to position 117, 150, 186, 191, 270, 568 or 578 of the wild-type ATP-gated ion channel P2X7R as depicted in SEQ ID NO: 3 or 4 is replaced by another amino acid residue; and

(ii) an epitope specifically presented by a polypeptide which has an amino acid sequence of an ATP-gated ion channel P2X7R, wherein amino acids corresponding to positions 488 to 494 of the wild-type ATP-gated ion channel P2X7R as depicted in SEQ ID NO: 3 or 4 are deleted.

15. The use of claim 11 or 14, wherein said antibody is a monoclonal antibody.

16. The use of claim 11, wherein said primer or pair of primers is selected from the group consisting of SEQ ID NOs.: 52 to 111.

17. The use of any one of claims 11 to 16, wherein the diagnostic composition optionally further comprising suitable means for detection.

18. A method of diagnosing an affective disorder or a susceptibility to an affective disorder comprising the step of determining in a sample obtained from an individual whether the P2XR7 protein expressed in the cells of said individual is non-functional, shows an altered ATP-gating in comparison to the wild-type P2XR7 protein or is over- or under-expressed in comparison to the P2XR7

protein level an unaffected individual.

19. A method for diagnosing an affective disorder or a susceptibility to an affective disorder comprising the step of determining in a sample obtained from an individual whether the P2X7R gene sequence or encoded protein thereof comprises a mutation in comparison to the wild-type P2X7R sequence.

20. The method of claim 19, wherein said mutation is a mutation as defined in claim 11.

21. The method of claim 20, wherein the occurrence of the mutation in the ATP-gated ion channel P2X7R gene is determined by PCR or immunological methods.

22. The use of any one of claims 11 to 17 or the method of any one of claims 18 to 21, wherein said affective disorder is selected from the group consisting of major depression, generalized anxiety disorder and bipolar disorder.

23. The use or the method of claim 22, wherein said major depression is selected from the group consisting of major depression, dysthymia, atypical depression, premenstrual dysphoric disorder and seasonal affective disorder.

24. The use or the method of claim 22, wherein said generalized anxiety disorder is selected from the group consisting of panic disorder, phobias, agoraphobia, social phobia, specific phobia, obsessive-compulsive disorder, post-traumatic stress disorder, separation anxiety disorder, mania, hypomania and cyclothymic disorder.

25. The use or the method of claim 22, wherein said bipolar disorder is bipolar disorder type I or bipolar disorder type II.

26. A method for diagnosing an affective disorder of an individual comprising:

(a) isolating DNA from cells obtained from an individual;

(b) determining all or part of the nucleotide composition of the P2X7R gene; and

(c) analyzing said nucleotide composition of P2X7R for the presence of one or more polymorphism(s) mutation or allelic variation.

27. A method for diagnosing an affective disorder of an individual comprising:

(a) isolating RNA from cells obtained from an individual;

(b) converting said RNA into cDNA;

(c) determining all or part of the nucleotide composition of the P2X7R gene; and

(d) analyzing said nucleotide composition of P2X7R for the presence of one or more polymorphism(s), mutation or allelic variation.

28. A method for diagnosing an affective disorder of an individual comprising:

(a) isolating RNA or protein from cells obtained from an individual ;

(b) determining the levels of P2X7R RNA or protein; and

(c) comparing the levels of P2X7R RNA or protein with the corresponding levels from a normal individual not afflicted with an affective disorder.

29. A diagnostic composition for use in diagnosis of an affective disorder comprising the nucleic acid molecule as defined in claim 11, 12 or 13, the vector as defined in claim 11, the polypeptide as defined in claim 11, the antibody as defined in claim 11, 14 or 15, the aptamer as defined in claim 11 and/or the primer or pair of primers as defined in claim 11 or 16.